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IFW 1636

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/903,640
Filing Date	JULY 11, 2001
First Named Inventor	AVI ASHKENAZI
Group/Art Unit	1636
Examiner Name	KATCHEVES, KONSTANTINA T.
Total Number of Pages in This Submission: 20	Attorney Docket Number: 39780-1618 P2C48

ENCLOSURES *(check all that apply)*

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [x] **AMENDMENT / RESPONSE**
- [ ] After Final
- [ ] Version With Markings Showing Changes
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Copy of Notice
- [ ] Copy of an Assignment
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [x] **ADDITIONAL ENCLOSURE(S)** ***(PLEASE IDENTIFY BELOW):***
- [x] **COPY OF ARTICLE BY BEER, ET AL.; and STAMPED RETURN POSTCARD**

Remarks

AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT 08-1641 FOR ANY FEES DUE IN CONNECTION WITH THIS PAPER, REFERENCING ATTORNEY'S DOCKET NO. 39780-1618 P2C48.

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

Firm or Individual name	HELLER EHRMAN LLP	PANPAN GAO (Reg. No. 43,626)	
	275 Middlefield Road, Menlo Park, California 94025	Telephone: (650) 324-7000	Facsimile: (650) 324-0638
Signature			
Date	NOVEMBER 9, 2005	Customer Number:	35489

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated below and addressed to: **MAIL STOP AMENDMENT,** Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450, on this date: **NOVEMBER 9, 2005**

Express Mail Label **EV 765 989 469 US**

Typed or printed name	C. FONG		
Signature	C. F	Date	NOVEMBER 9, 2005

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop ___, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Katcheves, Konstantina T.
Avi ASHKENAZI, et al.	)	Art Unit: 1636
Application Serial No. 09/903,640	)	Confirmation No. 3104
Filed: July 11, 2001	)	Attorney's Docket No. 39780-1618 P2C48
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

EXPRESS MAIL LABEL NO. EV 765 989 469 US
DATE MAILED: NOVEMBER 9, 2005

AMENDMENT AND RESPONSE TO OFFICE ACTION

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed on August 9, 2005 in connection with the above-identified patent application (Paper No./Mail Date 0522), please enter the following amendments, and consider the following arguments. This response is timely filed within the shortened statutory period set for the response hence no fees are believed due. Enclosed is a copy of article by Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) for the Examiner's reference, consideration of which is respectfully requested.

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims:

1-43. (canceled)

44. (previously presented) An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 263;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors.

45. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263.

46. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide.

47. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263.

48. (canceled)

49. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481.

50. (previously presented) A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.

51. (previously presented) The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

REMARKS/ARGUMENTS

Claims 44-47 and 49-51 are pending in this application. The rejections to the claims are respectfully traversed.

Claim Rejections-35 U.S.C. §§101/112, First Paragraph

Claims 44-47 and 49-51 are rejected under 35 U.S.C. §101, allegedly because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

Claims 44-47 and 49-51 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejection. With respect to Claims 44-47 and 49-51, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO343 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

Applicants have asserted utility for the instantly claimed PRO343 polypeptide based on amplification of the PRO343 gene in the "gene amplification assay" described in the instant specification in Example 92. Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 230-234 of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO343 showed

ΔCt values of approximately 1.00-3.62 in seven lung tumors and 1.15-3.49 thirteen colon tumors. This corresponds to at least **2.00- 12.3 fold amplification in lung tumors** and at least **2.22- 11.24 fold amplification in colon tumors**. Accordingly, the present specification clearly discloses strong evidence that the gene encoding the PRO343 polypeptide is significantly amplified in a significant number of lung and colon tumors.

In further support for the "significance" of the amplification, Applicants had submitted, in their Response filed March 11, 2003, a Declaration by Dr. Audrey Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO343 is a diagnostic marker of lung or colon cancer.

The Examiner notes that "the present claims are drawn to the polypeptide PRO343, not the polynucleotide" and therefore, there is allegedly, no specific, credible or substantial utility for the claimed polypeptides. The Examiner quotes Chen *et al.* to support this view.

Applicants submit that they had presented supportive evidence with their response mailed August 11, 2004 to show that the art generally teaches that "it is more likely than not" for amplified genes to also result in increased mRNA and protein levels. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, collectively teach that in general, gene

amplification increases mRNA expression. For instance, Ornitoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Ornitoft *et al.* showed a clear correlation between mRNA and protein expression levels in the proteins they studied and state that, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornitoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

Similarly Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants further submit that, contrary to the Examiner's assertion, the cited Chen *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO343 polypeptide. For instance, Applicants note that the proteins selected for their study in Chen *et al.* were identified by staining of 2D gels. As is well known, there are problems with selecting proteins detectable by 2D gels: "It is apparent that without prior enrichment only a relatively small and highly selected population of *long-lived, highly expressed proteins* is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is

the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus, Chen *et al.*, by selecting proteins visualized by 2D gels, are likely to have excluded in their analysis many key regulatory proteins which could be candidate cancer markers.

Secondly, the manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Once again, Applicants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper, Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) (copy enclosed) which described gene expression of genes in adenocarcinomas

and compared that to protein expression. In this paper they report that "these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression." (pg 317). The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma." Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

As was discussed in the Utility standard submitted in previous responses, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. Accordingly, the data by Chen *et al.* confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's Utility rejection is based on a misrepresentation of the scientific data presented in Chen *et al.* and by applying an improper, heightened legal standard in this case. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the mRNA and the encoded protein will also be expressed at an elevated level. As noted even in Chen *et al.* most genes showed a correlation between increased mRNA and translated protein.

The Examiner also notes that "the claimed sequences merely revealed similarity to proteases in genenral" (page 3, last paragraph of Office action). Applicants respectfully assert that utility for the instant PRO343 is based on the results in the gene amplification assay, not on structure prediction, and hence such a rejection is moot.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Omtoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration and the widespread use of array chips, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO343 gene, that the PRO343 polypeptide is concomitantly overexpressed.

Thus, Applicants have demonstrated utility for the PRO343 polypeptide based on the gene amplification assay and thus, Applicants request that the Examiner reconsider the utility for the present application based on the present arguments. Furthermore, since the specification has provided detailed protocols for the gene amplification assay, for example, in Example 92, one of ordinary skill in the art could identify that the claimed polypeptides could be made and used in the diagnosis of lung or colon tumors, without any undue experimentation.

Hence Applicants respectfully request reconsideration and reversal of the utility/ enablement rejection of the pending claims under 35 U.S.C. §§101/112, first paragraph.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C48**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 9, 2005

By:_____
Panpan Gao (Reg. No. 43,626)

HELLER EHRMAN, LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2166627 v1
11/9/05 11:15 AM (39780.1618)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re application of:	) Examiner: Ketter, James
Avi ASHKENAZI, et al.	) Art Unit: 1636
Application Serial No. 09/903,640	) Confirmation No. 3104
Filed: July 11, 2001	) Attorney's Docket No. 39780-1618 P2C48
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	) **Customer No. 35489**

EXPRESS MAIL LABEL NO. EV 765 978 214 US
DATE MAILED: AUGUST 15, 2006

PRELIMINARY RESPONSE

MAIL STOP: RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In the above identified application, a Final Office Action was mailed on February 22, 2006 and a response was timely filed before the two month date on April 20, 2006, with a Declaration by Dr. Paul Polakis (with attached Exhibits A and B). No Advisory Action was mailed. A Notice of Appeal was filed on May 22, 2006 with required fees.

This Preliminary Response accompanies a Request for Continued Examination (RCE) under 37 CFR §1.114 for the above identified application, and is filed with a petition for a one-month extension of time with necessary fees.

This submission is accompanied by a Declaration under 37 C.F.R. §1.132 by Dr. Randy Scott and with an Information Disclosure Statement, with copies of additional references in support of the Applicants' arguments. Applicants respectfully request that the previous response, the Polakis Declaration, the Information Disclosure Statement and the Scott Declaration be made of record in the above-identified application, and be considered by the Examiner.

Pending Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Pending Claims:

1-43. (canceled)

44. (previously presented) An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 263;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors.

45. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263.

46. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide.

47. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263.

48. (canceled)

49. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481.

50. (previously presented) A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.

51. (previously presented) The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

DECLARATION OF RANDY SCOTT, Ph.D. UNDER 37 C.F.R. § 1.132

I, Randy Scott, Ph.D. declare and say as follows:

1. I hold a Bachelor or Science degree in Chemistry from Emporia State University and a Ph.D. in Biochemistry from the University of Kansas.

2. I am Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company founded in August of 2000 located in Redwood City, California, conducting sophisticated genomic research to develop clinically validated molecular diagnostics, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy.

3. In 1991, I co-founded Incyte Pharmaceuticals, Inc., the world's first genomic information business. I served the company in multiple capacities, including Chairman of the Board from August 2000 to December 2001, President from January 1997 to August 2000, and Chief Scientific Officer from March 1995 to August 2000. Under my leadership, Incyte has created the LifeSeq Gold® gene sequence and expression database, an industry standard and the most comprehensive collection of biological information in the world. I have also led Incyte to expand its focus beyond gene sequence databases to include the research and application of gene expression, SNPs (single nucleotide polymorphisms), and proteomics.

4. I am an inventor on several issued patents, and authored over 40 scientific publications in the fields of protein biology, gene discovery, and cancer.

5. My Curriculum Vitae is attached to and serves part of this Declaration.

6. All statements made in this Declaration are based on my more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and my familiarity with the relevant art.

7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given

mRNA molecule to hybridize to the DNA template from which it originated. By using an array containing many DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is ~~precisely measured, generating a profile of gene expression in the sample.~~

8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be over-expressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

9. Correlation between mRNA and protein levels can be assessed by a variety of methods suitable for measuring protein expression levels, including, for example, SDS-polyacrylamide gel electrophoresis (SDS-PAGE), two-dimensional fluorescence-difference gel electrophoresis (DIGE), mass spectrometric approaches, microsequencing, and a combination of these and similar known techniques, however, direct measurement of protein expression levels remains non-trivial.

10. One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Patent.

Date: August 11, 2006

Randy Scott, Ph.D.

SV 2202107 v1
8/11/06 11:00 AM (39766.7000)

Randy W. Scott, Ph.D.
Genomic Health
301 Penobscot
Redwood City, CA 94022

EDUCATION:

1979 B.S., Chemistry, Emporia State University, Emporia Kansas
1983 Ph.D., Biochemistry, University of Kansas, Lawrence Kansas

WORK EXPERIENCE:

2000-present **GENOMIC HEALTH, INC., Cofounder**

- *Chairman & CEO, (2000-present)*
  Founded a new genomics company and raised over $100 million to bring personalized medicine to clinical practice. Selected by Red Herring Magazine as one of the Top 100 private technology companies in North America in 2005

1991-2000 **INCYTE, Cofounder**

- *Chairman of the Board (2000-2001)*
  Helped lead the transition to a new management team and transition to drug development
- *President and Chief Scientific Officer (1997-2000)*
  Responsible for Research & Development, Operations, Marketing & Sales. Built the world's first genomic information business with peak sales of over $200 million per year including 19 out of the worlds top 20 pharmaceutical companies as subscribers
- *Vice President and Chief Scientific Officer (1991-1997)*
  Built recombinant DNA therapeutic product portfolio and led the launch of the genomics business

1985-91 **INVITRON CORPORATION**

- *Sr. Director of Research (1998-1991)*
  Responsible for Research & Development.
- *Director of Protein Biochemistry (1985-1988)*
  Responsible for building the protein purification group for a cGMP manufacturing facility producing recombinant proteins, including monoclonal antibodies, tPA and Factor VIII.

1983-85 **UNIGENE LABORATORIES, Fairfield, New Jersey**

- *Sr. Scientist, Dept. of Protein Biochemistry*
  Led effort to work on IgA proteases linked to meningococcal infections

OTHER EXPERIENCE:

2005- Present **AMERICAN CLINICAL LABORATORY ASSOCIATION**

- *Member, Board of Directors*

1997-2000 **DIADEXUS, INC., Cofounder**

- *Member, Board of Directors, (1997-2000)*
  Worked with George Poste (CSO, SmithKline, Beecham) to establish a diagnostics joint venture between Incyte and SmithKline

Awards:

2001 Genome Technology Magazine 2001 All-Star
1999 Forbes Magazine list of Biotech's Top 25 Influential Insiders

1997 Ernst & Young/NASDAQ Silicon Valley Entrepreneur of the Year for Life Sciences
1987 Small Business Innovation Research Grant Award (Principal Investigator): "Azurophil-Derived Bactericidal Factor" Grant # SSS-5 (K) 1R43AI24409-011987
1983 Phillip Newmark Research Award, University of Kansas, 1983
1982 Borgendale Graduate Seminar Award, University of Kansas.

Publications:

Low, D.A., Cunningham, D.D., **Scott, R.W.**, and Baker, J.B., "Interactions of Serine Proteases with Human Fibroblasts: Regulation by Protease Nexin, A Cellular Component with Similarities to Antithrombin III." in Receptor-Mediated Binding and Internalization of Toxins and Hormones (Middlebrook, J.L. and Kohn, L.S. eds.) pp. 259-270, Academic Press, New York (1982).

Low, D.A., **Scott, R.W.**, Baker J.B., and Cunningham, D.D., Cells Regulate their Mitogenic Response to Thrombin through Release of Protease Nexin. Nature 298, 476-478 (1982).

Scott, R.W. ,"Purification, Characterization, and Functional Studies of Protease Nexin." Ph.D. Thesis, University of Kansas (1983).

Scott, R.W., Eaton, D.L., Duran, N. and Baker, J.B. Regulation of Extracellular Plasminogen Activator by Human Fibroblasts. The Role of Protease Nexin. J. Biol. Chem. 258, 4397-4403 (1983).

Scott, R.W., and Baker, J.B., Purification of Human Protease Nexin. J.Biol. Chem. 258, 10439-10444 (1983).

Eaton, D.L., **Scott, R.W.**, and Baker, J.B., Purification of Human Fibroblast Urokinase Proenzyme and Analysis of its Regulation by Proteases and Protease Nexin. J. Biol. Chem. 259, 6241-6247 (1984).

Scott, R.W., Bergman, B., Bajpai, A., Hersh, R., Rodriquez, H., Jones, B.N., Barreda, C., Watts, S., and Baker, J.B. Protease Nexin: Properties and a Modified Purification Procedure. J.Biol. Chem. 7029-7034 (1985).

Bergman, B.L., **Scott, R.W.**, Bajpai, A., Watts, S., and Baker, J.B., Inhibition of Tumor-Cell Extracellular Matrix Destruction by a Fibroblast Proteinase Inhibitor, Protease Nexin I. Proc. Nat. Acad. Sci. 83, 996-1000 (1986).

Cance, W.G., Wells, S.A., Dilley, W.G., Welch, M.J., Otsuka, F.L., **Scott, R.W.**, and Davie, J.M., Unique Parathyroid Membrane Antigen(s): Radiolocalization with Specific Monoclomal Antibodies. Surgical Form 37, 410-412 (1986).

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Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses Thereof

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Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,308,834 Issued May 3, 1994
Treatment of Endotoxin-Associated Shock and Prevention Thereof Using BPI Protein

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-I

U.S. Patent #5,234,912 Issued August 10, 1993
Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule Encoding Human Protease Nexin

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-1

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Basophil Granule Proteins

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U.S. Patent #6,372,431 Issued April 16, 2002
Mammalian Toxicological Response Markers

U.S. Patent #6,553,317 Issued April 22, 2003
Relational database and system for storing information relating to biomolecular sequences and reagents

The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte AUDREY GODDARD, PAUL J. GODOWSKI, AUSTIN L. GURNEY, VICTORIA SMITH, and WILLIAM I. WOOD

Appeal 2006-1469
Application 10/123,212
Technology Center 1600

Decided: April 30, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges.*

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 72-79 and 82-84. We have jurisdiction under 35 U.S.C. § 6(b). Claims 72 and 77 are representative of the claims on appeal, and read as follows:

72. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577,

wherein the nucleic acid encoding said polypeptide is overexpressed in colon, lung or prostate tumor cells.

77. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO:14;

(b) the amino acid sequence of the polypeptide of SEQ ID NO:14, lacking its associated signal peptide; or

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577.

Claims 72-79 and 82-84 stand rejected under 35 U.S.C. § 101 as not being supported by either a specific and substantial utility or a well-established utility. Claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification, and claims 72-76, 83, and 84 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Finally, 72-74, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Young,[1] and claims 72-75, 83, and 84 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Stanton.[2]

We Affirm-In-Part.

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[1] Young, US Patent No. 6,525,174 B1, issued February 25, 2003.
[2] Stanton, US Pub. No. 2002/0110804 A1, published August 15, 2002.

UTILITY

ISSUE

The Examiner contends that the Specification fails to establish a specific and substantial utility or a well-established utility of the polypeptide of SEQ ID NO:14.

Appellants contend that Example 30 presents microarray data demonstrating that the polypeptide of SEQ ID NO:14 is a diagnostic marker for colon, lung, and prostate tumors.

The issue is thus whether the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility or a well-established utility for the polypeptide of SEQ ID NO:14?

FACTS

The Examiner rejected claims 72-79 and 82-84 under 35 U.S.C. § 101 as not being supported by either a specific and substantial asserted utility or a well-established utility (Answer 4).

The Examiner notes that the Specification discloses the polypeptide of SEQ ID NO:14 (PRO1866), the nucleic acid sequence encoding it (SEQ ID NO:13), as well as antibodies against the polypeptide. (*Id.*)

As to a well-established utility, the Examiner asserts that the prior art does not demonstrate that the polypeptide of SEQ ID NO:14, the nucleic acid encoding the polypeptide or an antibody that binds to the polypeptide, has "any well-established biological functions or any physiological significance." (*Id.* at 4-5.)

Next, as to a specific and substantial utility, the Examiner references Table 8 of the Specification, which states that the polypeptide is

significantly overexpressed in colon, lung, or prostate tumors compared to a non-cancerous human tissue control. (*Id.* at 5.) The Examiner also notes that the statement is based on a microarray analysis, which measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. (*Id.*) According to the Examiner:

> There is no sufficient information or experimental data presented on whether the polypeptide or the nucleic acid of the present invention can serve as a reliable diagnostic marker for colon, lung or prostate tumors; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of colon, lung or prostate tumors without undue experimentation. Accordingly, the results in Table 8 obtained based upon the assay described in Example 30 only serve as the beginning point for further research on the biological functions or physiological significance of the polypeptide of SEQ ID NO:[]14 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

(*Id.* at 5-6.)

Appellants argue that patentable utility is demonstrated by Example 30 of the Specification (Br. 4). According to Appellants, Example 30 demonstrates that the gene encoding the polypeptide of PRO1866 (SEQ ID NO:14) "showed significant overexpression in colon, lung, and prostate tumors as compared to a universal normal control," demonstrating "'that the PRO polypeptides of the present invention are useful . . . as diagnostic markers for the presence of one or more cancerous tumors . . . .'" (*Id.*)

Appellants argue further that it is legally incorrect for the Examiner to require specific data, statistical analysis, and further details before accepting the utility set forth in the Specification, as the law is clear that the Examiner must accept Appellants' assertion of utility if that assertion would be credible to one of ordinary skill. (*Id.* at 4-5.)

Appellants assert that the Examiner has used an improper standard in asserting that mRNA levels do not necessarily correlate with the protein level and that protein levels cannot be accurately predicted from mRNA levels. (*Id.* at 6.) The evidentiary standard to be used during examination is preponderance of the evidence under the totality of the circumstances, and thus, Appellants argue, the Examiner "must establish that it is *more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility," which "is a much lower standard than a 'necessary' correlation or 'accurate' prediction, and is clearly met for the invention claim." (*Id.* (emphasis in original)).

Moreover, Appellants rely on the Declaration of Dr. Paul Polakis, which states that "*in general, there is a correlation between mRNA levels and polypeptide levels.*" (Br. 6 (emphasis in original)). Appellants also rely on the Declaration of Dr. Victoria Smith, which states that "*microarray analyses actually performed in my laboratory* have shown that when molecules are identified as being overexpressed in a human tumor sample of epithelial origin relative to the 'universal normal control'[3] sample, *in a majority of cases*, that molecule is also confirmed as being overexpressed in

[3] The "universal" epithelial control sample is prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung (Br. 12).

the human tumor tissue sample relative to its human tissue counterpart" (Br. 6 (emphasis in original)). Appellants aver that the two declarations support the assertion of utility in the Specification, *i.e.*, that the PRO1866 polypeptide (SEQ ID NO:14) "is reasonably expected to be overexpressed in colon, lung and prostate tumors and can be used as a cancer diagnostic marker." (*Id.* at 6-7.)

The Specification is drawn to the identification and isolation of novel DNA and to the recombinant production of polypeptides (Specification 1).

Example 30 on page 134 of the Specification is drawn to microarray analysis to detect PRO polypeptides in cancerous tumors.

According to the Specification:

> In the present example, cancerous tumors derived from various human tissues were studied for PRO polypeptide-encoding gene expression relative to non-cancerous human tissue in an attempt to identify those PRO polypeptides which are overexpressed in cancerous tumors. Two sets of experimental data were generated. In one set, cancerous human colon tumor tissue and matched non-cancerous human colon tumor tissue from the same patient ("matched colon control") were obtained and analyzed for PRO polypeptide expression using . . . microarray technology. In the second set of data, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test:control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering

> of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.
>
> In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the tumor tissues listed above were used for the hybridization thereto. A value based upon the normalized ratio:experimental ratio was designated as a "cutoff ratio". Only values that were above this cutoff ratio were determined to be significant. Table 8 below shows the results of these experiments, demonstrating that various PRO polypeptides of the present invention are significantly overexpressed in various human tumor tissues as compared to a non-cancerous human tissue control. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

(*Id.* at 134-35.)

As to PRO1866, the Specification presents Table 8, which states that PRO1866 is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. (*Id.* at 135.)

The Declaration of Dr. Paul Polakis, dated September 9, 2005, states in paragraphs 4 and 5 that, based on experience with other gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, it has been observed "that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the

level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells."

The Declaration of Dr. Victoria Smith at paragraph 5, dated September 9, 2005, states that the comparison of mRNA expression levels in human tumor tissues to mRNA expression levels in a sample prepared by pooling non-cancerous human tissues of epithelial origin "is extremely informative and provides a strong basis for the diagnostic determination of cancer in humans."

PRINCIPLES OF LAW

The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to

satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*, 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

ANALYSIS

We find that the microarray data presented in Example 30 of the Specification is sufficient to establish a specific and substantial utility for the polypeptide of SEQ ID NO:14, and the rejection is reversed.

The microarray data demonstrates that mRNA for the PRO1866 polypeptide (SEQ ID NO:14) is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. Thus, the polypeptide of SEQ ID NO:14 has a significant and presently available benefit to the public as a tumor marker.

We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.

Finally, the use of the PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility, and there is no requirement that a causative

link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors be demonstrated.

ENABLEMENT

ISSUE

The Examiner contends that the disclosure does not enable one skilled in the art to practice the full genus of peptides encompassed by Appellants' claims.

Appellants contend that one skilled in the art could practice the full scope of the claimed invention, as the skilled artisan has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:14, and the specification provides ample guidance such that one of skill in the art could readily test the nucleic acid encoding a variant polypeptide to determine whether it is overexpressed in colon, lung or prostate tumors by the methods set forth in Example 30.

Thus, the issue is does the Specification enable one skilled in the art to use the full scope of the PRO1866 (SEQ ID NO:14) variants of claim 72 without an undue amount of experimentation?